IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Christian P. Larsen et al.	**Examiner:**	Not yet known
Serial No.:	10/057,288	**Group Art Unit:**	1646
Filed:	January 25, 2002	**Docket No.:**	D0136NP/30436.58USU1
Title:	METHODS OF INDUCING ORGAN TRANSPLANT TOLERANCE AND CORRECTING HEMOGLOBINOPATHIES		

CERTIFICATE UNDER 37 CFR 1.8:
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on January 15, 2003.

By: Renato Marco P. Domingo

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b)(3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Information Disclosure Statement is being filed herein as a supplement to Applicant's July 31, 2002, Information Disclosure Statement which was submitted under 37 C.F.R. §1.97(b)(3) before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. §1.98(d), copies of Exhibits 137-207 as set forth in the Form 1449 are included herein.

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- International Publication No. WO95/33770 published December 14, 1995 – **Exhibit 137**
- International Publication No. WO02/02638 A2 published January 10, 2002 – **Exhibit 138**
- Linsley, Peter S. et al., "CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" *The Journal of Experimental Medicine*, 1991, 174:561-9 – **Exhibit 139**

- Gimmi, Claude D. et al., "Human T-cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" *Proc. Natl. Acad. Sci. USA*, 1993, 90:6586-90 – **Exhibit 140**
- Azuma, Miyuki et al., "B70 antigen is a second ligand for CTLA-4 and CD28" *Nature*, 1993, 366:76-9 – **Exhibit 141**
- Ronchese, Franca et al., "Mice Transgenic for a Soluble Form of Murine CTLA-4 Show Enhanced Expansion of Antigen-specific $CD4^+$ T Cells and Defective Antibody Production In Vivo" *The Journal of Experimental Medicine*, 1994, 179:809-17 – **Exhibit 142**
- Griggs, Nathan D. et al., "The Relative Contribution of the CD28 and gp39 Costimulatory Pathways in the Clonal Expansion and Pathogenic Acquisition of Self-reactive T Cells" *The Journal of Experimental Medicine*, 1996, 183:801-10 – **Exhibit 143**
- Verwilghen, Jo et al., "Expression of Functional B7 and CTLA4 on Rheumatoid Synovial T Cells" *The Journal of Immunology*, 1994, 153:1378-85 – **Exhibit 144**
- Blazar, Bruce R. et al., "In Vivo Blockade of CD28/CTLA4: B7/BB1 Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatibility Complex Barrier in Mice" *Blood*, 1994, 83:3815-25 – **Exhibit 145**
- Finck, Barbara K., et al., "Treatment of Murine Lupus with CTLA4Ig" *Science*, 1994, 265:1225-7 – **Exhibit 146**
- Perrin, Peter J. et al., "Role of B7:CD28/CTLA-4 in the Induction of Chronic Relapsing Experimental Allergic Encephalomyelitis" *The Journal of Immunology*, 1995, 154:1481-90 – **Exhibit 147**
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- Baliga, Prabhakar et al., "CTLA4Ig Prolongs Allograft Survival While Suppressing Cell-Mediated Immunity" *Transplantation*, 1994, 58:1082-90 – **Exhibit 149**
- Tepper, M. A. et al., "Tolerance Induction by Soluble CTLA4 in a Mouse Skin Transplant Model" *Transplantation Proceedings*, 1994, 26:3151-4 – **Exhibit 150**

Perico, Norberto et al., "Toward novel antirejection strategies: *In vivo* immunosuppressive properties of CTLA4Ig" *Kidney International*, 1995, 47:241-6 – **Exhibit 151**

- Finck, B. K. et al., "Effects of CTLA4Ig in Murine Lupus" *Arthritis and Rheumatism*, 1994, 37:S222 – **Exhibit 152**

Nishikawa, Kazuhiro et al., "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" *Eur. J. Immunol*, 1994, 24:1249-54 – **Exhibit 153**

- Wallace, Philip M. et al., "CTLA4Ig Treatment Ameliorates the Lethality of Murine Graft-Versus-Host Disease Across Major Histocompatibility Complex Barriers" *Transplantation*, 1994, 58:602-10 – **Exhibit 154**
- Damle, Nitin K. et al., "Costimulation of T Lymphocytes with Integrin Ligands Intercellular Adhesion Molecule-1 or Vascular Cell Adhesion Molecule-1 Induces Functional Expression of CTLA-4, a Second Receptor for B7" *The Journal of Immunology*, 1994, 152:2686-97 – **Exhibit 155**
- Milich, David R. et al., "Soluble CTLA-4 Can Suppress Autoantibody Production and Elicit Long Term Unresponsiveness in a Novel Transgenic Model," *The Journal of Immunology*, 1994, 153:429-35 – **Exhibit 156**
- Van Oosterhout, A. J. M. et al., "Murine CTLA4-IgG Treatment Inhibits Airway Eosinophilia and Hyperresponsiveness and Attenuates IgE Upregulation in a Murine Model of Allergic Asthma," *American Journal of Respiratory Cell and Molecular Biology*, 1997, 17:386-92 – **Exhibit 157**
- Abrams, Judith R. et al., "CTLA4Ig-mediated blockade of T-cell costimuation in patients with psoriasis vulgaris," *The Journal of Clinical Investigation*, 1999, 103:1243-52 – **Exhibit 158**
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- Wolfe, Frederick, "The epidemiology of drug treatment failure in rheumatoid arthritis," *Baillière's Clinical Rheumatology*, 1995, 9:619-32 – **Exhibit 163**
- Hochberg, Marc C. and Timothy D. Spector, "Epidemiology of Rheumatoid Arthritis: Update," *Epidemiologic Reviews*, 1990, 12:247-52 – **Exhibit 164**
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- Liu, Ming Fei, et al., "The Presence of Costimulatory Molecules CD86 and CD28 in Rheumatoid Arthritis Synovium," *Arthritis &Rheumatism*, 1996, 39:110-4 – **Exhibit 166**
- Sfikakis, Petros P. and Charles S. Via, "Expression of CD28, CTLA4, CD80, and CD86 Molecules in Patients with Autoimmune Rheumatic Diseases: Implications for Immunotherapy," *Clinical Immunology and Immunopathology*, 1997, 83: 195-8 – **Exhibit 167**
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- Racusen, Lorraine C., et al., "The Banff 97 working classification of renal allograft pathology," *Kidney International*, 1999, 55: 713- 23 – **Exhibit 169**
- Parkin, David, et al., "Treatment of multiple sclerosis with interferon β: an appraisal of cost-effectiveness and quality of life," *J. Neurol. Neurosurg. Psychiatry*, 2000, 68:144-9 – **Exhibit 170**
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- Thomas, Ranjeny and Christopher Quinn, "Functional Differentiation of Dendritic Cells in Rheumatoid Arthritis: Role of CD86 in the Synovium," *The Journal of Immunology*, 1996, 156:3074-86 – **Exhibit 173**
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- Schiff, Michael, "Emerging Treatments for Rheumatoid Arthritis" *Am. J. Med.*, 1997, 102: 11S-15S – **Exhibit 175**
- Balsa, A. et al., "Differential Expression of the Costimulatory Molecules B7.1 (CD80) and B7.2 (CD86) in Rheumatoid Synovial Tissue," *British Journal of Rheumatology*, 1996, 35:33-7 – **Exhibit 176**
- Ranheim, Erik A. and Thomas J. Kipps, "Elevated Expression of CD80 (B7/BB1) and Other Accessory Molecules on Synovial Fluid Mononuclear Cell Subsets in Rheumatoid Arthritis," *Arthritis &Rheumatism*, 1994, 37:1637-46 – **Exhibit 177**
- Freeman, Gordon J. et al., "Cloning of B7-2: A CTLA-4 Counter-Receptor That Costimulates Human T Cell Proliferation," *Science*, 1993, 262:909-11 – **Exhibit 178**
- Lakkis, Fadi G. et al., "Blocking the CD28-B7 T Cell Costimulation Pathway Induces Long Term Cardiac Allograft Acceptance in the Absence of IL-4," *The Journal of Immunology*, 1997, 158:2443-8 – **Exhibit 179**

  Pearson, Thomas C. et al., "Analysis of the B7 Costimulatory Pathway in Allograft Rejection," *Transplantation*, 1997, 63:1463-9 – **Exhibit 180**
- Alexander, Diane Z. et al., "Analysis of a Functional Role for Chimerism in CTLA4-Ig Plus Bone Marrow-Treaded Cardiac Allograft Recipients," *Transplantation*, 1994, 91:416-8 – **Exhibit 181**
- Larsen, Christian P. et al., "CD40-gp39 Interactions Play a Critical Role During Allograft Rejection," *Transplantation*, 1996, 61:4-9 – **Exhibit 182**

- Pearson, Thomas C. et al., "CTLA4-Ig Plus Bone Marrow Induces Long-Term Allograft Survival and Donor-Specific Unresponsiveness in the Murine Model," *Transplantation*, 1996, 61:997-1004 – **Exhibit 183**
- Weber, C. J. et al., "CTLA4-Ig Prolongs Survival of Microencapsulated Rabbit Islet Xenografts in Spontaneously Diabetic Nod Mice," *Transplantation Proceedings*, 1996, 28:821-3 – **Exhibit 184**
- Alexander, D. Z. et al., "Analysis of effector mechanisms in murine cardiac allograft rejection," *Transplant Immunology*, 1996, 4:46-8 – **Exhibit 185**
- Larsen, Christian P. et al., "Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways," *Nature*, 1996, 381:434-8 – **Exhibit 186**
- Elwood, Eric T. et al., "Microchimerism and rejection in clinical transplantation," *The Lancet*, 1997, 349:1358-60 – **Exhibit 187**
- Larsen, Christian P. and Thomas C. Pearson, "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Current Opinion in Immunology*, 1997, 9:641-7 – **Exhibit 188**
- Konieczny, Bogumila T. et al., "IFN-γ Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Constimulation Pathways," *The Journal of Immunology*, 1998, 160:2059-64 – **Exhibit 189**
- Elwood, Eric T. et al., "Prolonged Accpetance of Concordant and Discordant Xenografts with Combined CD40 and CD28 Pathway Blockade," *Transplantation*, 1998, 65:1422-8 – **Exhibit 190**
- Niimi, Masanori et al., "The Role of the CD40 Pathway in Alloantigen-Induced Hyporesponsiveness In Vivo," *The Journal of Immunology*, 1998, 161:5331-7 – **Exhibit 191**
- Bingaman, Adam W. et al., "Vigorous Allograft Rejection in the Absence of Danger," *The Journal of Immunology*, 2000, 164:3065-71 – **Exhibit 192**
- Bingaman, Adam W. et al., "Transplantation of the Bone Marrow Microenvironment Leads to Hematopoietic Chimerism Without Cytoreductive Conditioning," *Transplantation*, 2000, 69:2491-6 – **Exhibit 193**

- Bingaman, Adam W. et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology*, 2000, 8:195-202 – **Exhibit 194**
- Meng, L. et al., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings*, 2001, 33:418-20 – **Exhibit 195**
- Guo, Zhong et al., "CD8 T Cell-Mediated Rejection of Intestinal Allografts is Resistant to Inhibition of the CD40/CD154 Costimulatory Pathway," *Transplantation*, 2001, 71:1351-4 – **Exhibit 196**
- Ha, Jongwon et al., "Aggressive skin allograft rejection in $CD28^{-/-}$ mice independent of the CD40/CD40L costimulatory pathway," *Transplant Immunology*,2001, 9:13-7 – **Exhibit 197**
- Bingaman, Adam W. et al., "Analysis of the CD40 and CD28 Pathways on Alloimmune Responses by $CD4^{+}$ T Cells In Vivo," *Transplantation*, 2001, 72:1286-92 – **Exhibit 198**
- Adams, Andrew B. et al., "Calcineurin Inhibitor—Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates," *Diabetes,* 2002, 51:265-70 – **Exhibit 199**
- Whelchel, J. D. et al. "Evolving Strategies in Immunosuppressive Therapy: The Emory Experience," *Clinical Transplants*, 1996, J. Michael Cecka, Ph.D. and Paul I. Terasaki, Ph.D., (eds.), 249-55 – **Exhibit 200**
- Ritchie, Shannon C. et al., "Regulation of Immunostimulatory Function and B7 Molecule Expression on Murine Dendritic Cells," *Journal of Cellular Biochemistry*, 1995, 21A:C1-215 – **Exhibit 201**
- Alexander, Diane Z. et al., "Analysis of the Mechanisms of CTLA4-Ig Plus Bone Marrow Induced Transplantation Tolerance," *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 – **Exhibit 202**
- Alexander, Diane Z. et al., "CTLA4-Ig-Induced Transplantation Tolerance: Analysis of Donor Cell Chimerism," *Surgical Forum*, 1994, 45:402-4 – **Exhibit 203**
- Pearson, Thomas C. et al., "CTLA4-Ig + Bone Marrow Induces Transplantation Tolerance in the Murine Model," *Journal of Cellular Biochemistry*, 1995, 21A:C1-327 – **Exhibit 204**

- Lakkis, Fadi G. et al., "CTLA4Ig Induces Longterm Cardiac Allograft Survival in the Absence of Interleukin-4," *Journal of the American Society of Nephrology*, 1996, 7:1887 – **Exhibit 205**
- L104EA29Y (Figure 15, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
- L104EA29Y (Figure 15 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
  - L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
  - L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
- A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 206**.
  - The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
  - The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
  - The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 206), which differs from CTLA4Ig at two amino acid residues, Leu_{104}-Glu and Ala_{29}-Tyr (Exhibit 206 at page 2).

- An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 207**.
  - The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
  - The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
  - The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 207), but not the sequence of L104EA29Y (Figure 15, of the subject application).

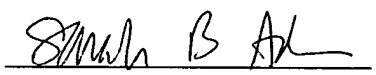
This statement should be considered because it is submitted before the mailing date of the first Office Action on the merits according to 37 C.F.R. §1.97(b)(3). In accordance with 37 C.F.R. §1.98(d), copies of Exhibit 1-136 are not provided herein as they have been previously provided before. Copies of Exhibits 137-207 are provided herein.

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that the references have been thoroughly reviewed or that any relevance of any portion of a reference is intended.

Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. § 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 50-0306.

Respectfully submitted,



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FORM 1449*	Docket Number	Application Number
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	D0136NP/30436.58USU1	10/057,288
	Applicant: Christian P. Larsen et al.	
(Use several sheets if necessary)	Filing Date: January 25, 2002	Group Art Unit: 1646

U.S. PATENT DOCUMENTS						
EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS							
	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	WO95/33770 (**Exhibit 137**)	12/14/95	PCT				X
	WO02/02638 A2 (**Exhibit 138**)	12/14/95	PCT				X

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)		
		Linsley, Peter S. et al., "CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" *The Journal of Experimental Medicine*, 1991, 174:561-9 (**Exhibit 139**)
		Gimmi, Claude D. et al., "Human T-cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" *Proc. Natl. Acad. Sci. USA*, 1993, 90:6586-90 (**Exhibit 140**)
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EXAMINER	DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.

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	D0136NP/30436.58USU1	10/057,288
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	Christian P. Larsen et al.	
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(Use several sheets if necessary)	January 25, 2002	1646

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	Applicant: Christian P. Larsen et al.	
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		Schiff, Michael, "Emerging Treatments for Rheumatoid Arthritis" *Am. J. Med.*, 1997, 102: 11S-15S **(Exhibit 175)**
		Balsa, A. et al., "Differential Expression of the Costimulatory Molecules B7.1 (CD80) and B7.2 (CD86) in Rheumatoid Synovial Tissue," *British Journal of Rheumatology*, 1996, 35:33-7 **(Exhibit 176)**
		Ranheim, Erik A. and Thomas J. Kipps, "Elevated Expression of CD80 (B7/BB1) and Other Accessory Molecules on Synovial Fluid Mononuclear Cell Subsets in Rheumatoid Arthritis," *Arthritis &Rheumatism*, 1994, 37:1637-46 **(Exhibit 177)**
		Freeman, Gordon J. et al., "Cloning of B7-2: A CTLA-4 Counter-Receptor That Costimulates Human T Cell Proliferation," *Science*, 1993, 262:909-11 **(Exhibit 178)**
		Lakkis, Fadi G. et al., "Blocking the CD28-B7 T Cell Costimulation Pathway Induces Long Term Cardiac Allograft Acceptance in the Absence of IL-4," *The Journal of Immunology*, 1997, 158:2443-8 **(Exhibit 179)**
		Pearson, Thomas C. et al., "Analysis of the B7 Costimulatory Pathway in Allograft Rejection," *Transplantation*, 1997, 63:1463-9 **(Exhibit 180)**
		Alexander, Diane Z. et al., "Analysis of a Functional Role for Chimerism in CTLA4-Ig Plus Bone Marrow-Treaded Cardiac Allograft Recipients," *Transplantation*, 1994, 91:416-8 **(Exhibit 181)**
		Larsen, Christian P. et al., "CD40-gp39 Interactions Play a Critical Role During Allograft Rejection," *Transplantation*, 1996, 61:4-9 **(Exhibit 182)**
		Pearson, Thomas C. et al., "CTLA4-Ig Plus Bone Marrow Induces Long-Term Allograft Survival and Donor-Specific Unresponsiveness in the Murine Model," *Transplantation*, 1996, 61:997-1004 **(Exhibit 183)**
		Weber, C. J. et al., "CTLA4-Ig Prolongs Survival of Microencapsulated Rabbit Islet Xenografts in Spontaneously Diabetic Nod Mice," *Transplantation Proceedings*, 1996, 28:821-3 **(Exhibit 184)**
		Alexander, D. Z. et al., "Analysis of effector mechanisms in murine cardiac allograft rejection," *Transplant Immunology*, 1996, 4:46-8 **(Exhibit 185)**
		Larsen, Christian P. et al., "Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways," *Nature*, 1996, 381:434-8 **(Exhibit 186)**

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FORM 1449*	Docket Number	Application Number
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	D0136NP/30436.58USU1	10/057,288
	Applicant: Christian P. Larsen et al.	
(Use several sheets if necessary)	Filing Date: January 25, 2002	Group Art Unit: 1646

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)		
		Elwood, Eric T. et al., "Microchimerism and rejection in clinical transplantation," *The Lancet*, 1997, 349:1358-60 **(Exhibit 187)**
		Larsen, Christian P. and Thomas C. Pearson, "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Current Opinion in Immunology*, 1997, 9:641-7 **(Exhibit 188)**
		Konieczny, Bogumila T. et al., "IFN-γ Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Constimulation Pathways," *The Journal of Immunology*, 1998, 160:2059-64 **(Exhibit 189)**
		Elwood, Eric T. et al., "Prolonged Accpetance of Concordant and Discordant Xenografts with Combined CD40 and CD28 Pathway Blockade," *Transplantation*, 1998, 65:1422-8 **(Exhibit 190)**
		Niimi, Masanori et al., "The Role of the CD40 Pathway in Alloantigen-Induced Hyporesponsiveness In Vivo," *The Journal of Immunology*, 1998, 161:5331-7 **(Exhibit 191)**
		Bingaman, Adam W. et al., "Vigorous Allograft Rejection in the Absence of Danger," *The Journal of Immunology*, 2000, 164:3065-71 **(Exhibit 192)**
		Bingaman, Adam W. et al., "Transplantation of the Bone Marrow Microenvironment Leads to Hematopoietic Chimerism Without Cytoreductive Conditioning," *Transplantation*, 2000, 69:2491-6 **(Exhibit 193)**
		Bingaman, Adam W. et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology*, 2000, 8:195-202 **(Exhibit 194)**
		Meng, L. et al., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings*, 2001, 33:418-20 **(Exhibit 195)**
		Guo, Zhong et al., "CD8 T Cell-Mediated Rejection of Intestinal Allografts is Resistant to Inhibition of the CD40/CD154 Costimulatory Pathway," *Transplantation*, 2001, 71:1351-4 **(Exhibit 196)**
		Ha, Jongwon et al., "Aggressive skin allograft rejection in $CD28^{-/-}$ mice independent of the CD40/CD40L costimulatory pathway," *Transplant Immunology*,2001, 9:13-7 **(Exhibit 197)**
		Bingaman, Adam W. et al., "Analysis of the CD40 and CD28 Pathways on Alloimmune Responses by $CD4^+$ T Cells In Vivo," *Transplantation*, 2001, 72:1286-92 **(Exhibit 198)**
		Adams, Andrew B. et al., "Calcineurin Inhibitor—Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates," *Diabetes*, 2002, 51:265-70 **(Exhibit 199)**
		Whelchel, J. D. et al. "Evolving Strategies in Immunosuppressive Therapy: The Emory Experience," *Clinical Transplants*, 1996, J. Michael Cecka, Ph.D. and Paul I. Terasaki, Ph.D., (eds.), 249-55 **(Exhibit 200)**
		Ritchie, Shannon C. et al., "Regulation of Immunostimulatory Function and B7 Molecule Expression on Murine Dendritic Cells," *Journal of Cellular Biochemistry*, 1995, 21A:C1-215 **(Exhibit 201)**
		Alexander, Diane Z. et al., "Analysis of the Mechanisms of CTLA4-Ig Plus Bone Marrow Induced Transplantation Tolerance," *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 **(Exhibit 202)**
		Alexander, Diane Z. et al., "CTLA4-Ig-Induced Transplantation Tolerance: Analysis of Donor Cell Chimerism," *Surgical Forum*, 1994, 45:402-4 **(Exhibit 203)**
		Pearson, Thomas C. et al., "CTLA4-Ig + Bone Marrow Induces Transplantation Tolerance in the Murine Model," *Journal of Cellular Biochemistry*, 1995, 21A:C1-327 **(Exhibit 204)**
		Lakkis, Fadi G. et al., "CTLA4Ig Induces Longterm Cardiac Allograft Survival in the Absence of Interleukin-4," *Journal of the American Society of Nephrology*, 1996, 7:1887 **(Exhibit 205)**

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INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	D0136NP/30436.58USU1	10/057,288
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(Use several sheets if necessary)	Filing Date: January 25, 2002	Group Art Unit: 1646

		OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		• L104EA29Y (Figure 15, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
		• L104EA29Y (Figure 15 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
		  • L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
		  • L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
		• A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 206.**
		  • The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
		  • The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
		  • The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 206), which differs from CTLA4Ig at two amino acid residues, Leu_{104}-Glu and Ala_{29}-Tyr (Exhibit 206 at page 2). **(Exhibit 206)**

		• An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 207.**
		  • The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
		  • The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
		  • The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 207), but not the sequence of L104EA29Y (Figure 15, of the subject application). **(Exhibit 207)**

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